REMARKS

Applicants respectfully request reconsideration and further examination of all pending claims presented herein.

I. Telephonic Interview

The undersigned attorney would like to thank the Examiner for the time spent on December 18, 2008 discussing the pending claims and the Office action of July 3, 2008. The Interview Summary dated December 24, 2008 has been noted and, to the extent necessary, is further discussed herein below.

The Applicants respectfully submit that while a discussion was made regarding whether the Manual, Pet-Radiopharmaceutical Dispensing Unit and its corresponding Supplement were ever published prior to the priority date of the present application, the undersigned does not recollect affirmatively committing to contact the company that prepared the manual and supplement regarding its publication date. While an inquiry may be made by the Applicants, it is respectfully submitted that the burden is on the Office, not on the Applicant, to verify that a document that is being cited against an application.

II. Status of the Claims

In this Amendment C, claims 1, 2, 4, 5, 11, 15 and 16 have been amended to address minor typographical errors therein, and/or for purposes of clarification only. Additionally, claims 17 and 18 have been added to more particularly claim certain embodiments. Support for claim 18 may be found in claim 5 as originally filed, while support for claim 17 may be found, for example, in paragraph [0004] of the published application (U.S. Publication No. 2005/017553).

Accordingly, claims 1, 2, 4-18 are now pending. Claims 6-15 have been withdrawn for being directed to a non-elected invention and/or species. Claims 1, 2, 4, 5 and 16-18 are therefore currently under examination.

III. Rejection under 35 U.S.C. §103(a)

Reconsideration is requested of the rejection under 35 U.S.C. §103 of claims 1, 2, 4, 5 and 16 as being obvious based on the combination of the Supplement to the Manual and Operating Instructions, FDG Synthesizers, Nuclear Interface GmbH, in view of Damhaut et al. (U.S. 6,172,207), and further in view of Asai et al. (U.S. 5,536,491) and Stone-Elander et al. (U.S. 5,308,944).

A. Status of the Manual PET-Radiopharmaceutical Dispensing Unit and FDG Synthesizers Supplement to the Manual and Operating Instructions As Prior Art

In view of the comments made in the Interview Summary of December 24, 2008, and the Office action of July 3, 2008, it is noted that Office cites this Manual and Supplement for disclosing the heating of fluor-deoxy-glucose (FDG) with a buffer to a temperature of 135°C. However, without commenting on the disclosure provided by these documents and/or the Office's view thereof, Applicants respectfully point out the following:[1]

> (i) A reference is proven to be a printed publication upon a **satisfactory showing** that the reference has been disseminated or otherwise made available to the extent that interested persons of ordinary skill in the subject matter or art, exercising reasonable diligence, can locate it. (See, e.g., MPEP §2128.) In this instance, no evidence has been provided to show that the cited documents were so disseminated or otherwise made available. The cited documents were submitted by a third party during examination of the analogous or related European Patent Application (Application No. 03 721 834.4–2123, Publication No. EP 1496946). No additional documentation or evidence was provided with the cited documents, to support any assertion that these documents were disseminated or otherwise made available. In fact, the European Examiner concluded, before finding the pending claims of the noted European patent application patentable, that there was simply **insufficient evidence** to support the conclusion that these documents were disseminated or otherwise made available to the public. The Examiner noted, in particular, that the circumstances of the alleged distribution, or publication, where not substantiated sufficiently.
>
> (ii) Furthermore, it is to be noted that the mere listing of a reference in an information disclosure statement is not to be viewed as an admission that the reference is prior art against the pending claims. (See, e.g., MPEP §2128.) Accordingly, the mere fact that Applicants submitted the noted references in an information disclosure statement, after they were submitted in the above-noted European patent application, does not mean Applicants believe these documents are prior art.

[1] Although Applicants have not commented on the substance of the noted references herein, they respectfully reiterate the statements made previously, in Amendment B and/or during the above-noted telephonic interview.

In view of the foregoing, Applicants respectfully submit that the cited documents do not qualify as prior art against the present application. As a result, Applicants will direct the remainder of their comments on the present rejection toward the combination of Damhaut et al., Asai et al. and Stone-Elander et al., only.

B. The Claimed Subject Matter

Claim 1, from which all other pending claims depend either directly or indirectly, is directed to a method for improving radiostability of a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution during autoclaving. The method comprises the steps of: (a) providing a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution, and (b) adding at least one buffer based on a weak acid to the a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution. As indicated in the specification (see, e.g., paragraphs [0003-0004] of the published application, U.S. Publication No. 2005/017553), Applicants have discovered a method for preparing a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution that is sufficiently sterile and stable for use (i.e., for injection in a patient in need thereof). Sterilization is achieved by autoclaving a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution that has been sufficiently buffered with a solution of a weak acid. In this way, a sterilized solution is obtained that maintains acceptable radiochemical purity eight hours after production.

C. Damhaut et al.

It is noted that Damhaut et al. disclose the preparation of ^{18}F-fluor-deoxy-glucose (^{18}F-FDG). However, as previously noted (see, e.g., Applicants' Amendment B, dated April 17, 2008), they are not concerned with the preparation of a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution that possess stability sufficient to withstand sterilization by autoclaving. In fact, Damhaut et al. **do not even reference autoclaving**. Rather, Damhaut et al. disclose the use of filtration in order to purify and sterilize their ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution. (See, e.g., column 5, lines 44-48 and Applicants' Amendment B at page 7 discussing same.)

D. Asai et al.

The Office asserts that Asai et al. disclose the sterilization of ^{19}F-labeled MRI contrast agents via autoclaving, pointing specifically to Example 30 therein. However, even assuming *arguendo* this is correct, Applicants respectfully point out that a **^{19}F-labeled MRI** contrast agent is distinctly different from a **^{18}F-labeled radionuclide**. These compounds are being used for entirely different purposes, and function in entirely different ways. More specifically:

(i) 19F is not a radioisotope which undergoes radioactive decay, emitting ionizing radiation that can result in radiolysis of molecules to which it is attached.

(ii) MRI, or magnetic resonance imaging, utilizes magnetic fields and imaging agent that include a paramagnetic metal. Notably, therefore, the compounds disclosed by Asai et al. include a paramagnetic metal (designated "Me" by Asai et al. in the claimed contrast medium).

(iii) Radiological imaging methods utilize a radionuclide, or a radioisotope such as ^{18}F, that undergoes radioactive decay, and in the process emits gamma rays and/or subatomic particles, which constitute ionizing radiation that may be detected. As a result, a paramagnetic metal is not needed in the compounds of the present disclosure.

(iv) Additionally, and consistent with the foregoing, it is to be noted that the ^{18}F isotope used in the present disclosure has a half-life or undergoes a decay that is distinctly different from that of the non-radioactive ^{19}F isotope present in the compounds of Asai et al.

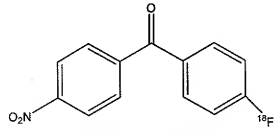
(v) The compounds of the present disclosure are based on glucose, whereas the compounds of Asai et al. are based on a cyclic polyamine.

(vi) Finally, the success or failure of autoclaving a non-radioactive ^{19}F-cyclic polyamine molecule used in MRI procedures would not suggest to one skilled in the art that a radioactive ^{18}F-FDG solution comprising a weak acid could be autoclaved wherein radiochemical purity is maintained in acceptable pharmacologic concentrations due to the presence of the weak acid in the ^{18}F-FDG solution.

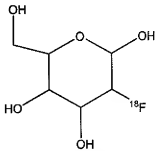
In view of the foregoing, Applicants submit Asai et al. is simply not relevant to the subject matter of the present invention; that is, Applicants submit that Asai et al. is **not analogous art** to the present invention.

E. Stone-Elander et al.

The Office appears to cite Stone-Elander et al. for disclosing that the ^{18}F isotope of the compounds disclosed therein will be stable when subjected to elevated temperatures. However, even assuming *arguendo* this is correct, Applicants respectfully point out that Stone-Elander et al. disclose the use of an ^{18}F isotope in the context of a 4-nitro-4-fluorobenzophenone compound, which as illustrated below is structurally very different from the ^{18}F-fluoro-2-deoxy-glucose compound used in the present invention.



4-nitro-4'-fluorobenzophenone



^{18}F-fluor-deoxy-glucose

Furthermore, **no reference is made by Stone-Elander et al. to subjecting their disclosed compounds to an elevated temperature in an autoclave.**

F. The Claimed Subject Matter is Not Obvious

As set forth in MPEP §2143, in order for the Office to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art references, when combined, must teach each and every element of the claim; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references; and (3) there must be some reasonable expectation of success. Applicants respectfully submit the Office has failed to establish a prima facie case of obviousness because there is **no motivation to modify** the references in order to achieve the claimed subject matter.

As stated above, the instant claims embodies the discovery of a method that renders ^{18}F-fluoro-2-deoxy-glucose sufficiently stable, such that it may undergo sterilization by autoclave, by adding at least one buffer based on a weak acid thereto. With respect to the cited references, Applicants note that:

(i) The cited Manual and Supplement **do not qualify as prior art**;

(ii) Asai et al. **is not relevant or analogous art** for the reasons set forth above, and in particular is not relevant or analogous art because it involves a different isotope (^{18}F v. ^{19}F), a different core structure or molecule (glucose v. cyclic polyamine), and a different use or application (radiochemical application v. MRI, including the fact that the Asai et al. compounds include a paramagnetic metal and the compounds used in the present invention do not).

(iii) Damhaut et al., while being directed to a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution, discloses a different approach to purification and sterilization. Specifically, Damhaut et al. disclose the use of filtration to purify and sterilize their compounds **and make no reference** to autoclaving the compounds.

(iv) Finally, while Stone-Elander et al. arguably disclose the thermal stability of a ^{18}F isotope, it is in **completely different** compounds, which are structurally unrelated to glucose. Specifically, the compounds of Stone-Elander et al. include two phenyl rings linked by a carbonyl carbon, and further include a nitro substituent. In contrast, the glucose-based compounds used in the method of the present invention are not aromatic, but rather are 6-member oxygen-containing heterocycles and include multiple hydroxyl substituents rather than a nitro substituent. As a result, the compounds of Stone-Elander et al. are also **completely different** and structurally unrelated to the compounds disclosed by Damhaut et al. Furthermore, Stone-Elander et al. make no reference to autoclaving.

In view of the foregoing, Applicants respectfully submit there is **simply no motivation to modify** the cited references in order to arrive at the claimed subject matter. Specifically, there is no motivation to modify the disclosure of Damhaut et al. with that of Asai et al. because the subject matter of Asai et al. is clearly unrelated to that of Damhaut et al. or the present invention. Furthermore, there is no motivation to modify the disclosure of Damhaut et al. with that of Stone-Elander et al., because the compounds of Stone-Elander et al. are clearly unrelated to those of Damhaut et al. or the present invention. Applicants respectfully submit that if one of ordinary skill in the art were motivated to modify the disclosure of Damhaut et al. in order to arrive at a different method of purification and sterilization, such a person would look to references involving: (i) radionuclides, rather than the MRI imaging agents and methods disclosed by Asai et al., and (ii) other heterocyclic compounds, rather than compounds that include multiply aromatic rings, none of which include a heteroatom.

In view of the foregoing, Applicants respectfully submit that the Office has failed to meet its burden in establishing a prima facie case of obviousness. Accordingly, reconsideration of the rejection of claim 1 is respectfully requested.

Inasmuch as claims 2, 4, 5 and 16 depend directly or indirectly from claim 1, Applicants submit these claims are not obvious for at least the same reasons as those set forth with respect to claim 1. Therefore, reconsideration of the rejection of these claims is also requested.

CONCLUSION

In view of the foregoing, Applicants request favorable reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge Deposit Account No. 13-1160 for any fees that may be required for this Amendment C, including the fee associated with a three (3) month extension of time and the Request for Continued Examination being filed simultaneously herewith.

Respectfully Submitted,

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